U.S. Department of Justice

Drug Enforcement Administration

Washington, D.C. 20537

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Docket Management Branch
(HFA-305)
Food and Drug Administration
12420 Parklawn Drive
Room 1-23
Rockville, Maryland 20857

Dear Sir:

This is in reference to Docket No. 98N-0148 regarding the inclusion of isomers, esters, ethers and analogues of all substances in Schedules I and II of the 1971 Convention. The Drug Enforcement Administration (DEA) has reviewed the available data regarding the above substances. These data could be incorporated into the critical reviews to be used for the 31st World Health Organization (WHO) Expert Committee on Drug Dependence.

Enclosed is DEA's response to the questionnaire submitted to Member States by the Secretary-General of the United Nations pertaining to all substances in Schedules I and II of the 1971 Convention. The DEA is pleased to be providing such data to the Food and Drug Administration for inclusion in the U.S. submission to WHO for its critical review and prereview documents.

Sincerely,

Judith K. Lawrence

for Frank L. Sapienza, Chief
Drug & Chemical Evaluation Section

Enclosures

98N-0148

CL

Questionnaire for data collection for use by WHO & CND of the Economic and Social Council of the United Nations

1. Is there any licit manufacture of:

a) isomers, esters, ethers, and salts thereof of any of the substances in Schedules I and II of the 1971 Convention.

Isomers

For the purposes of this questionnaire that the term "isomers" will mean enantiomers and diastereomers of psychotropic substances which are not included in Schedules I and II of the 1971 Convention. There are six substances for which this holds true:

(+)-cathinone
(-)-lysergic acid diethylamide (LSD)
(±)-isolysergic acid diethylamide (2 substances)
(±)-*trans*-4-methylaminorex (2 substances)

For the purposes of this questionnaire, manufacture is defined according to the 1971 Convention as "all processes by which psychotropic substances may be obtained".

In the US, (+)-cathinone, (-)-lysergic acid diethylamide, (±)-isolysergic acid diethylamide (geometric isomer of LSD), and *cis*-4 methylaminorex are Schedule I controlled substances. *trans*-4-Methylaminorex is not controlled under the CSA.

In the United States, cathinone, LSD, and (±)-*trans*-4-methylaminorex are licitly manufactured for research and reference standards. The manufacturers do not stipulate whether or not specific isomers of the above substances are produced. Both isomers of cathinone are available in the US for use as analytical reference materials. Isolysergic acid is also available for the same purpose.

Esters and Ethers

For the purposes of this questionnaire, the licit manufacture of esters and ethers of the following substances was investigated: DMHP; parahexyl; THC; the six isomers of THC listed in Schedule I; psilocin; zipeprol.

The DEA has no information pertaining to the licit manufacture of esters of the above substances.

Small quantities of methyl ethers and related analogues of Δ8-, Δ9- and Δ9,11-tetrahydrocannabinol were manufactured for pharmacological evaluation.. Ether analogues have

been manufactured for evaluation for their agonist and antagonist pharmacological properties in animal models.

b) a substance resulting from the modification of the chemical structure of substances already in Schedule I or II of the 1971 Convention?

For the purposes of this questionnaire, the term "analogues" will be utilized in place of the following phrase: "substances resulting from the modification of the chemical structure of substances already in Schedule I or II of the 1971 Convention". The definition of analogues will be similar to one utilized in the Controlled Substances Act (CSA) for the purposes of this questionnaire and will imply: a chemical structure similar to that of a controlled substance in Schedule I or II which produces a stimulant, depressant or hallucinogenic effect substantially similar to or greater than that produced by a Schedule I or II controlled substance.

The definition of amphetamine-like analogues would extend to substances such as ephedrine, pseudoephedrine, epinephrine, fenfluramine, dopamine...etc... that are utilized as licit pharmaceuticals, research substances and reference standards. These substances have an extensive legitimate market in the US. Using the above definitions, there would be hundreds of analogues of Schedule I and II psychotropic substances (See Shulgin, 1995). Many of these have been manufactured in small quantities in the United States for scientific and research activities. The following are some examples:

DEA has information pertaining to the licit manufacture of analogues and isomers of THC, from information submitted to DEA as part of research protocols and from information published in the scientific literature.

Six bromination products of the isomeric dimethoxyphenethylamines (hence, isomers of Nexus) were manufactured for analytical purposes in 1997.

For similar purposes, analogues of methoxy-MDA were synthesized from nutmeg oil and 3-methoxy-4,5-methylene-dioxybenzaldehyde (Clark et al, 1995).

A series of N-substituted 3,4-methylenedioxyphenyl-2-butanamines were synthesized for analytical and research purposes (Clark et al, 1995).

Metabolites and analogues of THC were prepared for research purposes (chemical synthesis, pharmacological evaluation) in the United States.

The methyl ether of bufotenine and hence a psilocin analogue was prepared for pharmacological evaluation and binding studies (Whitaker and Seeman, 1978).

p-Bromo and p-methoxy analogues of methylphenidate were manufactured (Thai et al, 1998) in the first reported asymmetric synthesis of methylphenidate and related substances.

Analogues of Δ8-tetrahydrocannabinols with conformationally more-defined sidechains were manufactured (Papahatjis et al, 1998).

Benzofuran, indan and tetralin analogues of MDMA were synthesized and analyzed for pharmacoloical activity (Monte et al, 1993).

2. Has any abuse been reported of: a) such isomers, esters, ethers or salts?

Isomers

The DEA has not received any reports of abuse of (-)-lysergic acid diethylamide, (±)-isolysergic acid diethylamide, or (±)-*trans*-4-methylaminorex.

Esters or Ethers

DEA has had no reports of abuse of esters or ethers of psychotropic substances. None of the substances that are listed in the DEA System To Retrieve Information from Drug Evidence (STRIDE) database are esters or ethers of psychotropic substances.

It is unlikely that ethers of the tetrahydrocannabinol isomers will present a significant abuse problem. Research reports indicate that certain ether analogues of the cannabinoid drug class have minimal in vivo activity. The reports indicate that the phenolic hydroxyl is important for receptor recognition and in vivo potency (Compton *et al*, 1991). Another report indicates the molecular conformation of the methyl ether of Δ9-THC is unlike that of Δ9-THC and has great impact on its biological activity (Reggio, 1987).

b) a substance resulting from the modification of the chemical structure (analogues) of substances already in Schedule I or II of the 1971 Convention?

For reasons of abuse and trafficking, the United States has controlled the following substances which can be defined as analogues of psychotropic substances:

- MBDB, a positional isomer of N-Ethyl MDA. Additionally, all other positional isomers of hallucinogenic substances in Schedule I of the CSA
- 4-bromo-2,5-dimethoxyphenethylamine
- 5-methoxy-3,4-methylenedioxyamphetamine
- bufotenine
- 1-[(1-thienyl)cyclohexyl]pyrrolidine & other PCP analogues
- N,N-dimethylamphetamine

3. What is the degree of seriousness of the public health and social problems associated with such abuse? Examples of public health and social problems are acute intoxication, accidents, work absenteeism, mortality, behaviour problems, criminality, etc.

By virtue of the pharmacological similarity to parent compounds, abuse of many of the above substances can be expected to result in public health and social problems such as acute intoxication, accidents, work absenteeism, mortality, behaviour problems, and criminality. The risk to the public health has been evaluated for substances such as N,N-dimethylamphetamine, 2C-B, and PCP analogues and is contained in the control documents which are available from the Drug Enforcement Administration upon request.

4. Have there been seizures of any such substances in the illicit traffic during the previous three years? If so, what quantities were involved?

Isomers

(+)-cathinone
(-)-lysergic acid diethylamide (LSD)
(±)-isolysergic acid diethylamide (2 substances)
(±)-trans-4-methylaminorex (2 substances)

For the time period, 1/1/95 to 12/31/97 seizures for the following substances were reported in the DEA System To Retrieve Information from Drug Evidence.

Substance Name	Number of Seizures
cathinone[a]	9
l-lysergide	0
l-isolysergide	0
4-methylaminorex	0

[a]isomers of cathinone not distinguished

Esters and Ethers

DEA does not have any information to demonstrate seizures of esters and ethers of psychotropic substances.

Analogues

The following information was reported in issues of Microgram, 1995-1997.

1. In 1997, An exhibit containing 0.1 g of white granular material was seized by the North Carolina Bureau of Investigation in Raleigh, North Carolina. The exhibit contained **5-methoxy-N,N-dimethyltryptamine** (an isomer of an ether of psilocin).

2. In 1997, the Forensic Science Service Metropolitain Laboratory in London, England reported the analysis of a number of tablets that contained **4-methylthioamphetamine** and caffeine. The tablets were mottled white, 14.0 mm in diameter, 4.7 mm thick and weighing 710 mg, single scored but with no other markings.

3. In 1995 and 1996, several seizures of tablets containing **MDEA (3,4-methylenedioxy-ethylamphetamine), MBDB (N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine)** and **MDMMA (N,N-dimethyl-3,4-methylenedioxyamphetamine)** that originated from Holland were noted in Italy. The tablets had different markings: 1) pink tablets with a Fido-Dido" figure containing MDEA and MBDB; 2) white tablets with a "$" figure containing MBDB; 3) beige tablets with a "bird" figure containing MDMMA.

4. In October 1996, the Florida Department of Law Enforcement, Orlando Regional Crime Laboratory seized two round white tablets with skull and crossbones on one side and "Killers" imprinted on the other side. The tablets contained round pink tablet with no markings that contained **MBDB (N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine)**.

5. In July 1996, the New Jersey State Police, East Regional Laboratory, in Sea Girt reported receiving several white colored tablets bearing a "$" logo. The tablets contained **MBDB (N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine)** on the basis of chemical analysis.

6. In June 1996, the Southwester Institute of Forensic Sciences in Dallas reported an exhibit of 19 white colored tablets bearing a "$" imprint. Each tablet measured 10 mm in diameter and had an average weight of 300 mg. The tablets contained **MBDB (N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine)** on the basis of chemical analysis.

7. In June 1996, the Utah Department of Public Safety Criminalistics Laboratory, Salt Lake City, recently encountered an exhibit consisting of 180 mg of off-white solid. Chemical analysis revealed methamphetamine, amphetamine and N,N-dimethylamphetamine, possible **Ephedra-based methamphetamine.**

8. In April 1996, the New Mexico Department of Public Safety Southern Crime Laboratory, Mesilla Park reported an exhibit consisting of an 87 mg lump of white material. Chemical analysis revealed methamphetamine, amphetamine and N,N-dimethylamphetamine, an indication that the exhibit was synthesized from **Ephedra** rather than ephedrine or pseudoephedrine.

9. In February 1996, The Metropolitan Police Forensic Science Laboratory, London, U.K.

reported a 1.5 kg exhibit of inhomogeneous orange powder which was identified as **1-(4-methylphenyl)ethylamine** by chemical analysis.

10. In October 1996, the Iowa Division of Criminal Investigation Criminalistics laboratory, Des Moines identified **MBDB (N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine)** tablets (several). The tablets were round, white and bore a "$" imprint.

11. In April 1996, the Israel National Police Division of Identification and Forensic Science in Jerusalem reported ten seizures totalling 150 tan, unscored tablets with "$" imprint that contained **MBDB (N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine)** by laboratory analysis.

12. In January 1995, the North Carolina Bureau of Investigation in Raleigh reported the seizure of two exhibits of **bufotenine** (0.2g and 0.5g, respectively).

13. In April 1995, the Florida Department of Law Enforcement Regional Crime Laboratory in Ft. Meyers reported the seizure of 44 grayish-white single scored tablets bearing an image of the cartoon character "Fido-Dido". The tablets contained **MBDB (N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine)** by laboratory analysis.

14. In July 1995, the Ministerio De Sanidad Y Consumo Laboratory in Barcelona, Spain reported several submissions of white, single scored tablets bearing the "Fido-Dido" cartoon character imprint. The tablets contained **MBDB (N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine)**. In another submission the laboratory received white, single scored tablets without the cartoon character impression that also contained **MBDB**.

15. In September 1995, the Israel National Police Division of Identification and Forensic Science reported a seizure of 61 off-white "Fido Dido" tablets which contained **MBDB (N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine)**.

16. In September 1995, the Health Department of Spain, Laboratory of Drugs in the Balearic Islands reported an exhibit received in 1994 consisting of 10 grayish white tablets bearing the "Fido Dido" character and which contained **MBDB (N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine)**.

17. In November 1995, the Carabinieri Investigazioni Scientifiche Sottocentro laboratoria di Chimica in Parma, Italy reported several exhibits consisting of white single scored tablets with the "Fido Dido" cartoon character imprint and which contained **MBDB (N-methyl-1-(3,4-methylene-dioxyphenyl)-2-butanamine)**. Some of the tablets also contained caffeine.

18. In November 1995, the Florida Department of Law Enforcement's Regional Crime Laboratory in Tallahassee reported an encounter of 14 tan colored unscored tablets imprinted with "$" and containing **MBDB (N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine)**.

19. In December 1995, the Ministerio de Sanidad Y Consumo, Laboratory de Drogas in Barcelona, Spain reported an exhibit of unscored tablets with "$" imprinted on one side which contained **MBDB (N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine)**.

20. In March 1998, the Virginia Division of Forensic Science in Norfolk reported exhibits consisting of white tablets with "Scrooge McDuck" logo containing **MBDB (N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine)** and unmarked dark green tablets containing MDMA, MDEA and Nexus (**4-bromo-2,5-dimethoxyphenethylamine**). They also report three submissions of white tablets with a "Fido Dido" logo containing **MBDB (N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine)**.

21. In March 1998, the Virginia Division of Forensic Science in Roanoke reported two exhibits consisting of dark red tablets containing **MBDB (N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine)** and caffeine.

The following information was obtained from the DEA STRIDE database for the time period 01/01/95 to 12/31/97

Substance seized	Number of Seizures
Bufotenine	2
Chloroephedrine	2
d-Lysergic acid amylamide	0
d-Lysergic acid butylamide	0
d-Lysergic acid diisopropyl amide	0
d-2-Bromolysergide	0
Dimethamphetamine	1
Dipropyltryptamine	0
Fenfluramine	74
l-Methylpsilocybin	0
Mescaline	7
N-Butyl-1-phenylcyclohexylamine	0
N-isobutyl-1-phenylcyclohexylamine	0
1-Phenylcyclohexylmorpholine	0

3,4-Dimethoxyamphetamine	0
MBDB	0
2C-B	6
Tryptamine	0

5. Were such seized substances identified as being of local or foreign manufacture? Did they have any commercial markings?

See question #4, seizures reported in *Microgram.*

6. Was there any detection of clandestine laboratories manufacturing such substances?

In 1995-1996, most of the clandestine laboratories seized in the United States were producing methamphetamine. There were also a small number of methcathinone, amphetamine and phenyl-2-propanone laboratories seized. In past years, however, the Drug Enforcement Administration has identified the illicit manufacture of 2C-B, N,N-dimethylamphetamine and other amphetamine and tryptamine analogues.

Summary

The DEA has had relatively few encounters with isomers, esters, ethers and analogues of Psychotropic Substances. This is due, in part, to the passage of the Controlled Substances Analogue Enforcement Act of 1985 (see attached document). This act amended the Controlled Substances Act to allow for the criminal prosecution of those persons who intentionally marketed or distributed a controlled substances analogue for the purposes of avoiding controlled substances laws. This provided the U.S. Drug Enforcement officials with a proactive response to the problem of designer-drug trafficking. The analogue provision of the Controlled Substances Act has proven to be a successful instrument for attacking the problem of analogues and similar legislation that is in accord with individual legal systems could be considered by other countries.

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CONTROLLED SUBSTANCE ANALOGUES

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Drug Enforcement Administration
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Introduction

During the 1980s the United States experienced a proliferation of the trafficking and abuse of illicitly produced substances, known as "designer drugs" or controlled substance analogues. Controlled substance analogues refer to substances of abuse that produce the "high" or euphoria of controlled substances (narcotics, stimulants, depressants and hallucinogens) but which have chemical structures slightly different from those of controlled substances. Because each individual substance was not specifically listed under the United States Controlled Substances Act (CSA), they were not subject to the provisions of this law at that time. Similarly, these types of substances were not controlled under international treaties unless specifically listed. Many of these substances were phenethylamine stimulants or ring-substituted amphetamine derivatives.

Controlled substance analogues are generally produced in clandestine laboratories by altering the synthesis of controlled substances. Either the immediate precursor or a reagent is altered to obtain the desired end-product. For example, the reaction of ephedrine with hydriodic acid and red phosphorus yields methamphetamine, while the reaction of phenylpropanolamine (PPA) with these same reagents yields amphetamine. Thus, the production of these analogues also may have an impact on chemical control programs since it is impossible to specifically list all precursors or reactants. By selling these analogues, traffickers avoided the penalties that would have been levied against those involved in the manufacture and distribution of controlled substances. This phenomenon seems to have diminished in the United States in recent years, in part, due to the enactment of legislation specifically targeting this activity. Available information indicates that Europe and other areas are currently experiencing a proliferation of analogues produced in illicit laboratories. Following is a description of the analogue phenomenon, as it occurred in the United States, and the initiatives taken to counteract it.

The Controlled Substance Analogue Phenomenon

The concept of designing pharmacologically active, chemically related substances is neither new nor restricted to illicit laboratories. In fact, most controlled substance analogues were not designed by clandestine chemists, but are substances that were developed by legitimate pharmaceutical chemists. Information about these substances was generally published in the scientific literature. In the quest for better medicinal agents, pharmaceutical companies synthesize and test numerous analogues of a parent compound to find the one with the most and best desirable effects and the least side-effects. Many of these analogues mimic the qualitative actions of the original compound, but may vary in potency, onset or duration of action. For example, consider the large number of variations within the benzodiazepine family of drugs, in which the parent drug is chlordiazepoxide (Librium). Many analogues of chlordiazepoxide (e.g., diazepam,

alprazolam, flunitrazepam, etc.) are now legitimately marketed and have similar therapeutic and psychoactive properties. There are an equally large number of phenethylamine analogues used therapeutically as well as for abuse purposes.

The illicit synthesis of analogues for the purpose of avoiding controlled substance laws also is not new. This phenomenon surfaced in the 1960s with the synthesis and distribution of ring-substituted amphetamine analogues such as 3,4-methylenedioxyamphetamine (MDA), 4-methyl-2,5-dimethoxyamphetamine (DOM/STP), 3,4,5-trimethoxyamphetamine (TMA), para-methoxyamphetamine (PMA), 4-bromo-2,5-dimethoxyamphetamine (DOB), and 2,5-dimethoxyamphetamine (DMA). Each of these hallucinogenic amphetamines was subsequently controlled individually under the CSA and the Convention on Psychotropic Substances, 1971. This clandestine laboratory activity in the United States was pivotal in the establishment of an administrative scheduling provision in the U.S. CSA. In the 1970's, analogues of phencyclidine (PCP) and methaqualone were controlled under the CSA after substantial quantities were illicitly produced, distributed and abused.

The more recent problem with controlled substance analogues in the United States occurred in the 1980s and centered around narcotic, stimulant and hallucinogenic analogues. Analogues of narcotics included variations on fentanyl and pethidine (meperidine). Fentanyl is a short-acting, highly potent substance used as an analgesic and anesthetic. Over ten fentanyl analogues, known as China White and synthetic heroin, with potencies of up to several thousand times that of fentanyl, were synthesized in illicit laboratories, distributed and responsible for scores of overdose deaths in the United States. Meperidine analogues included MPPP (1-methyl-4-phenyl-4-propionoxypiperidine) and PEPAP [1-(2-phenethyl)-4-phenyl-4-acetoxypiperidine]. Samples of MPPP also contained a neurotoxic by-product, MPTP (1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine) which is formed during the synthesis of MPPP. A number of individuals who used the MPPP/MPTP mixture developed a severe Parkinson's disease-like state as a consequence. Neurological damage produced by MPTP is irreversible and worsens with time.

Modification of the phenethylamine and amphetamine molecule has produced the most analogues identified in the illicit traffic. These modifications can lead to substances with pure central nervous system stimulant activity (e.g., methcathinone), hallucinogenic activity (e.g., 4-bromo-2,5-dimethoxyphenethylamine (2C-B)) or a combination of both depending upon the dose (e.g., 3,4-methylenedioxyamphetamine (MDA)). Changes to the phenyl ring may lead to substances with hallucinogenic activity while changes to the ethylamine chain usually result in varying levels of stimulant activity. The synthesis and activity of many of these analogues have been reviewed by Glennon (See "Synthesis and Evaluation of Amphetamine Analogues", in Clandestinely Produced Drugs, Analogues and Precursors, M. Klein, F. Sapienza, H. McClain, Jr. and I. Khan, Editors, 1989). Additional data on many of these substances can be found in a World Health Organization publication entitled Information Manual on Designer Drugs, Programme on Substance Abuse.

Several analogues of the hallucinogenic amphetamine, 3,4-methylenedioxyamphetamine (MDA) have been clandestinely manufactured and abused in the United States and around the world. These include 3,4-methylenedioxymethamphetamine (MDMA), 3,4-methylenedioxy-N-

ethylamphetamine (MDE), 3,4-methylenedioxy-N-hydroxyamphetamine, N-methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine (MBDB). Each produces effects similar, at least, in part, to MDA. Under the U.S. CSA, MBDB is controlled in Schedule I as a positional isomer of MDE. Other ring-substituted amphetamines or phenethylamines, such as 2C-B (4-bromo-2,5-dimethoxyphenethylamine) and PMMA (para-methoxymethamphetamine) have also been identified in the illicit traffic. Scores of similar substances are described by Shulgin (See Shulgin and Shulgin, in PIHKAL, A chemical Love Story, 1995)

Analogues of amphetamine and other central nervous system stimulants include N,N-dimethylamphetamine, methcathinone (Ephedrone), aminorex and 4-methylaminorex. Each has been produced in clandestine laboratories and identified in the illicit traffic in the United States and elsewhere.

U.S. Government Response

Until 1984, the United States had to rely on traditional administrative scheduling or legislative control to add a substance to the list of controlled substances. Traditional administrative scheduling under the U.S. CSA provides a role for both the law enforcement (DEA) and health (Department of Health and Human Services; DHHS) authorities. It involves the collection of all types of data by DEA, a scientific and medical evaluation of that data by DHHS and an independent evaluation by DEA. DEA must then make specific findings regarding the abuse potential, accepted medical use and safety and physical and psychological dependence potentials of the substance under review before determining its appropriate control status. The process allows for comments from interested parties and the opportunity for a hearing, if requested. Under the best of circumstances, this process takes six months to one year. If a hearing is requested it may take several years. The scheduling of MDMA, for example was initiated in 1984 and finalized in 1988. This was not an effective response against the analogue phenomenon.

In 1984, the U.S. Congress amended the CSA to include a provision for DEA to temporarily place a substance into Schedule I for a period of one year if it was found necessary to do so to avoid an imminent hazard to the public safety. This control could be extended one time for six months as long as procedures to permanently control the substance had been initiated. This procedure can not be applied to substances already controlled in another schedule and to marketed or investigational substances. DEA is not required to solicit or receive a scientific and medical evaluation from the health authorities, only to provide a notification of its intent to temporarily control the substance. DEA is required to consider the substance's history and current pattern of abuse, its scope, duration and significance of abuse, and its risk to the public health, in making a determination of whether the substance should be subject to emergency controls. Emergency scheduling imposes the full range of regulatory controls and criminal sanctions on the substance and those who handle it. DEA first used its emergency scheduling authority in April 1986 and has placed 21 substances under emergency control since then. These have included fentanyl and meperidine analogues, stimulant amphetamine analogues, hallucinogenic amphetamine analogues and a tryptamine analogue. These substances were placed into Schedule I on an emergency basis because of their appearance in the illicit drug traffic,

chemical similarity to known controlled substances, and known or predicted pharmacological similarity to controlled substances. When specific pharmacological data was not available, structure activity relationships formed an important basis for initial control. Once sufficient scientific data was obtained, permanent scheduling followed each of these emergency actions.

Although this emergency scheduling process greatly reduced the amount of time required to place a "new" substance under the CSA, clandestine laboratory operators continued to synthesize new analogues before the DEA could control them, even on an emergency basis. The emergency controls continued to be reactive and took a few months to complete. The U.S. government looked for a way to become proactive. Two basic alternatives were considered. The first was class scheduling. This would list chemical structural parameters for different classes of substances subject to abuse and control. All substances which fell within these parameters would be considered controlled. Defining these parameters was rather difficult for the many classes of controlled substances. Additionally, this method would impose regulatory controls on thousands of substances and could negatively impact legitimate drug development.

The second alternative was to impose only criminal sanctions on the activity of manufacturing and distributing an analogue intended for human consumption. This was the approach taken and in 1986, the CSA was again amended. The Controlled Substance Analogue Enforcement Act of 1986 (See attached) provided that a controlled substance analogue, to the extent intended for human consumption, could be treated as a Schedule I substance. It defined a controlled substance analogue as a substance which (1) has a chemical structure substantially similar to that of a controlled substance in Schedule I or II; (2) produces a stimulant, depressant or hallucinogenic effect substantially similar to or greater than that produced by a Schedule I or II controlled substance; or (3) is represented by an individual to produce such an effect. Again, marketed substances, or those under active investigation, are exempt from this provision. With this provision, analogues of controlled substances are covered under the criminal, but not the regulatory, provisions of the CSA. The requirement that analogues be intended for human consumption and the exemptions for marketed and investigational substances ensure that legitimate research and development are not hindered.

It is important to note that there is no list of controlled substance analogues. Whether a substance is a controlled substance analogue is determined at each criminal proceeding. Once a substance is permanently controlled under the CSA, there is little debate as to whether that substance is classified as a controlled substance and subject to the criminal provisions of the CSA. Individuals who are prosecuted for manufacture or distribution of a controlled substance analogue can force the prosecution to prove on each occasion to a judge and/or a jury that a substance meets the definition of a controlled substance analogue. Expert testimony may be heard in each criminal proceeding to determine if a substance meets the definition of a controlled substance analogue. Forensic chemists are used to describe the points of similarity between the structure of the analogue compared to that of a controlled substance. Biological data, if available, or structure activity relationships, are used to determine the pharmacological similarity between the controlled substance and the analogue. If an analogue is identified in the illicit traffic on several occasions, emergency controls are usually imposed and ultimately, the substance is permanently scheduled under the CSA.

The U.S. government has successfully prosecuted a substantial number of individuals under this provision for the manufacture and distribution of various analogues. These have included analogues of MDA, amphetamine, methamphetamine, meperidine, fentanyl and others. It appears that most, if not all, of the substances described in "PIHKAL" could meet the definition of controlled substance analogue, and if intended for human consumption, would fall under the analogue provision of the CSA. Individuals manufacturing and distributing these substances can and have been successfully prosecuted. Both the emergency scheduling and the analogue provisions of the CSA have withstood challenges in the courts.

Conclusion

An examination of the scheduling actions under the CSA since 1980 show that there were a large number of illicit substances (each could be considered an analogue) controlled and emergency scheduled in the 1980s (See attached). This activity has dramatically decreased since 1990 with only four substances placed under emergency control. Additionally there are currently no controlled substance analogues under review in the United States for emergency or permanent control. This decrease in the production and distribution of analogues can be attributed, at least in part, to the passage of the emergency and analogue provisions of the CSA, successful prosecutions under these provisions, and unsuccessful challenges to these statutes in the courts. Both of these statutes, but particularly the analogue statute, have proven to be successful and effective tools in attacking the problem of controlled substance analogues. Similar legislation, consistent with individual legal systems, should be considered by other countries.

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